

Amendments to the Specification:

Please REPLACE the first paragraph on page 1 with the following amended paragraph:

This application is a continuation of U.S. Serial No. 08/924,287, filed September 5, 1997, now allowed, which is a continuation-in-part of U.S. Serial No. 08/851,350, filed May 5, 1997, now [pending]U.S. Patent No. 6,057,122, which is a [continuation in part]continuation-in-part of U.S. Serial No. 08/832,087 filed April 3, 1997, now [pending]U.S. Patent No. 5,981,484, which is a continuation-in-part of U.S. Serial No. 08/643,219 filed May 3, 1996, now [pending]U.S. Patent No. 5,801,146.

Please REPLACE the paragraph at page 1, lines 9 through 15 with the following amended paragraph:

The present invention relates to the field of peptide chemistry. More particularly, the invention relates to the preparation and use of peptides containing amino acid sequences substantially similar to the corresponding sequences of the kringle 5 region of mammalian plasminogen, pharmaceutical compositions containing the peptides, antibodies specific for the [angiostatin]kringle 5 receptor, means for [angiostatin]kringle 5 detection and measurement, cytotoxic agents linked to [angiostatin]kringle 5 proteins and treatment of diseases which arise from or are exacerbated by angiogenesis.

Please REPLACE the paragraph at page 4, line 25 with the following amended paragraph:

[FIG. 1]Figures 1(a)-1(c) show[s] the amino acid sequence of human plasminogen (SEQ ID NO:1).

Please REPLACE the paragraph at page 4, lines 26-28 with the following amended paragraph:

[FIG. 2]Figures 2(a) and 2(b) show[s] the comparative homology in amino acid sequences of human (SEQ ID NO:34), mouse (SEQ ID NO:35), Rhesus monkey (SEQ ID NO:36), bovine (SEQ ID NO:37), and porcine (SEQ ID NO:38) kringle 5.

Please REPLACE the paragraph at page 4, line 29 with the following amended paragraph:

[FIG. 3] Figures 3(a) and 3(b) show[s] the DNA sequence (SEQ ID NO:12) of human plasminogen.

Please REPLACE the paragraph at page 8, line 18 with the following replacement paragraph:

A-Pro-Glu-Lys-Arg-Tyr-Asp-Tyr-Y (SEQ ID NO:39)

Please REPLACE the paragraph on page 46, line 12 with the following amended paragraph:

N-Ac-Pro-Arg-Lys-Leu-3-I-Tyr-Asp-Tyr-NH₂ (SEQ ID NO:[13]6)

Please REPLACE the paragraph on page 47, line 1 with the following amended paragraph:

N-Ac-Pro-Arg-Lys-Leu-Tyr-Asp-3-I-Tyr-NH₂ (SEQ ID NO:[14]18)

Please REPLACE the paragraph on page 47, lines 17-19 with the following amended paragraph:

Preparation and separation of a mixture N-Ac-Pro-Arg-Lys-Leu-Tyr-Asp-3-I¹²⁵-Tyr⁵³⁵-NH₂ and N-Ac-Pro-Arg-Lys-Leu-3-I¹²⁵-Tyr⁵³³-Asp-Tyr-NH₂ (SEQ ID NO:[13]6) and (SEQ ID NO:[14]18) respectively.

Please REPLACE the paragraph on page 50, lines 4-12 with the following amended paragraph:

The effect of kringle 5 peptide fragments on endothelial cell proliferation was determined *in vitro* using the above described endothelial cell proliferation assay. For these experiments, kringle 5 peptide fragments [was]were prepared as illustrated in Examples 1 through 14 and tested at various concentrations ranging from about 100 to 1000 pM with bFGF used as a maximum proliferation control. The kringle 5 peptide

fragment [SEQ ID NO: 3]from amino acids 535-543 of SEQ ID NO:1 was effective at inhibiting BCE cell proliferation in a dose-dependent manner. The concentration of [kringle 5 peptide fragment SEQ ID NO: 3]this fragment required to reach 50% inhibition (ED₅₀) was determined at about 300 pM. In contrast, the ED₅₀ of kringles 1-4 was shown to be 135 nM.

Please REPLACE Table 1 on page 51 with the following amended Table 1:

Table1

| Protein Fragment from SEQ ID NO: 1 | Antiproliferative Activity of BCE Cells (ED ₅₀) | Migratory Inhibition of HMVEC Cells (ED ₅₀) |
|--|---|---|
| kringles 1-4 (angiostatin)* | 135 nM | 160 nM |
| kringle 1 (Tyr ⁸⁰ -Glu ¹⁶³)* | 320 nM | - |
| kringle 2 (Glu ¹⁶¹ -Thr ²⁴⁵)* | no activity | - |
| kringle 3 (Thr ²⁵³ -Ser ³³⁵)* | 460 nM | - |
| kringle 4 (Val ³⁵⁴ -Val ⁴⁴³)* | no activity | - |
| kringles 1-3 (Tyr ⁸⁰ -Pro ³⁵³)* | 75 nM | 60 nM |
| kringles 2-3 (Glu ¹⁶¹ -Ser ³³⁵)* | - | - |
| kringle 5 (Val ⁴⁴³ -Ala ⁵⁴³) | 250 pM | 200 pM |
| kringle 5 (Val ⁴⁴⁹ -Ala ⁵⁴³) | - | 240 pM |
| kringle 5 (Val ⁴⁵⁴ -Ala ⁵⁴³) | - | 220 pM |
| kringle 5 (Val ⁴⁴³ -Phe ⁵⁴⁶) | 60 nM | 55 nM |
| kringle 5 (Val ⁴⁴⁹ -Phe ⁵⁴⁶) | - | - |
| kringle 5 (Val ⁴⁵⁴ -Phe ⁵⁴⁶) | - | - |
| kringles 4-5 (Val ³⁵⁵ -Ala ⁵⁴³) | - | 280 pM |
| kringles 4-5 (Val ³⁵⁵ -Phe ⁵⁴⁶) | - | - |
| N-Ac-Val ⁴⁴⁹ -Asp ⁴⁶¹ -NH ₂ | - | > 1 mM |
| N-Ac-Met ⁴⁶³ -Pro ⁴⁸² -NH ₂ | - | > 1 mM |
| N-Ac-Gln ⁴⁸⁴ -Tyr ⁵¹¹ -NH ₂ | - | >100 μM |
| N-Ac-Arg ⁵¹³ -Trp ⁵²³ -NH ₂ | - | 500 pM |
| N-Ac-Tyr ⁵²⁵ -Tyr ⁵³⁵ -NH ₂ | - | 200 pM |

| | | |
|---|---|----------|
| N-Ac-Pro ⁵²⁹ -Tyr ⁵³⁵ -NH ₂ | - | 120 pM |
| N-Ac-Pro ⁵²⁹ -Asp ⁵³⁴ -NH ₂ | - | 123 pM |
| N-Ac-Pro ¹⁵⁰ -Tyr ¹⁵⁶ -NH ₂ | - | 160 nM |
| N-Ac-Arg ⁵³⁰ -Tyr ⁵³⁵ -NH ₂ | - | 80 pM |
| N-Ac-Pro-Arg-Lys-Leu-3-I-Tyr- Asp-Tyr-NH ₂ | - | > 100 nM |
| N-Ac-Pro-Arg-Lys-Leu-Tyr-Asp- 3-I-Tyr-NH ₂ | - | 400 pM |
| N-Ac-Lys ⁵³¹ -[Tyr]Asp ⁵³⁴ -NH ₂ | - | - |